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CHRONIC STRESS AND PERFORMANCE

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ABSTRACT

Stressors are a natural component of life for all mammals. The stress response is a physiological reaction to stressors that may be amenable to change by a variety of situations. Chronic stressors in the form of social stressors, physical stressors, the combination of both social and physical stressors, and the administration of the stress hormone corticosterone have a variety of effects on various measures of animal performance. In particular, chronic stressors can affect spatial learning, anxiety, and depression. Several important themes emerged from a review of the pertinent literature on the effects of chronic stressors on rodent performance. Chronic stressors impact rodent performance in an inconsistent manner and several potential areas remain to be explored.

Keywords: Chronic stressors, stress response, rodent performance

1.0 CHRONIC STRESS AND PERFORMANCE

Stressors (such as predator stress, thermal stress, witness stress, or novel situations) are a natural component of life for all mammals. Furthermore, chronic stressors such as social stressors, physical stressors, or the administration of the stress hormone corticosterone have a variety of effects on measures of animal performance. This literature review explores the multitude of effects of chronic stressors on rodent performances of spatial learning, anxiety, and depression. The following review will be used to shape the stress-related research of the Bioscience and Performance Division.

2.0 WHAT IS STRESS?

2.1 The Evolution of Stress

Stress is a seemingly inevitable aspect of all life for animals and the effects of stress can influence a wide range of behaviors and bodily systems (Baum & Posluszny, 1999). No single definition of stress exists. The concept of stress involves a diversity of factors, and remains highly subjective and ambiguous in nature. Research in chronic stress has been hampered by the absence of an operational definition for that condition. A useful starting point for defining stress includes Cannon's (1932) description of *the fight-or-flight response*. He proposed that when an organism feels threatened by an external stimulus, the body responds by either attacking or fleeing from the threatening environment.

Selye (1956) provided another prominent contribution to stress research by developing the traditional psychosocial model of stress. He defined stress as nonspecific and described that a person who is subjected to repeated stress goes through three phases: alarm reaction, stage of

resistance, and exhaustion (i.e. the *general adaptation syndrome*). This general reaction to stress is viewed as a standard set of reactions that mobilize the organism's resources to deal with an impending threat. However, the definition of stress has morphed over the years to include the environment, a response state (psychological stress, distress, or eustress), or an internal interpretation of a stressor. For the sake of simplicity, stress refers to a negative emotional experience or condition accompanied by predictable physiological, biochemical, affective, cognitive, or behavioral changes that can affect well-being (Baum & Posluszny, 1999).

A more recent influential model on stress research includes the *tend-and-befriend* model (Taylor et al., 2000). This model proposes that animals, in addition to the fight-or-flight response, affiliate with each other and protect their offspring during stressful situations. This model benefits the family system, in comparison to the individualistic benefits of the fight-or-flight response. Thus, the tend-or-befriend model promotes the protective characteristics of belonging to a social group.

2.2 Systemic vs. Psychogenic Stressors

Two notable forms of stress include systemic and psychogenic stressors. Systemic stressors refer to stressors involving an immediate physiologic threat or a direct perceived disruption of homeostasis (Herman & Cullinan, 1997). Psychogenic stressors refer to stimuli that do not involve an immediate threat to homeostasis and require active cognitive processing (i.e. response to novelty, conditioned fear) (Ostrander, 2006). Thus, psychogenic stressors are a form of social stress, while systemic stressors are a response to stress.

2.3 The Stress Response vs. Stressors

The ability to cope or adapt to stressors is a fundamental necessity of life. Animals react to life stressors with a coordinated set of psychophysiological reactions known as the stress

response. The stress response is characterized by the fight-or-flight response, which includes increased startle reactivity, variations in cardiovascular functioning, changes in autonomic tone, and activation of neuroendocrine axes (Goldstein, 1996). This initial reaction to stressors can be adaptive because it readies the organism for a potential threat or strengthens the organism to respond more effectively for a future threat (Metz, 2001). Stressors are the stressful events themselves or the physical or psychological factors that cause the stress response. While stressful experiences can take a myriad of forms, their outcomes can be categorized as acute (short-term effects, usually adaptive) or chronic (long-term effects, usually maladaptive) (Bowman, Zrull, & Luine, 2001).

2.4 Allostasis vs. Allostatic Load

The adaptation mechanism that has evolved to handle acute stressors is known as *allostasis,* which remains imperative for maintaining homeostasis (McEwen, 1998). Meanwhile, prolonged exposures to stressors can produce an adaptation effect known as *allostatic load,* which refers to the deterioration of the body from chronic overuse (McEwen, 1998). Allostatic load can also occur if the allostatic systems fail to shut off after a stressful event is terminated or when these systems fail to respond to the initial challenge (resulting in over activity of other systems). Allostatic load can produce a myriad of adverse effects such as impaired health or an increased susceptibility to mental disorders (Gamaro, 1998; & Park, 2001). Selye (1936) also developed a classical stress theory on the General Adaptation Syndrome, where pathology develops from the exhaustion of adaptive mechanisms due to chronic stressors. Thus, acute stressors enhance the immune system, while chronic stressors can suppress the immune system (McEwen, 2000). This review will focus on chronic stress.

3.0 IMPORTANCE OF STUDYING STRESS

It is important to study stress in animals because the effects from life stressors play a role in the etiology of various mental disorders and experimental drug dependence (Van den Berg, Lamberts, Wolterink, Wiegant, & Van Ree, 1998). Chronic stressors can lead to the development of anxiety disorders (Adamec, Blundell, & Collins, 2001; Matuszewich, et al., 2007; Zelena, Haller, Halasz, & Makara, 1999) and mood disorders (Gregus, Wintink, Davis, & Kalynchuk, 2005; Joels, et al., 2004; Matuszewich, et al., 2007). Post-traumatic stress disorder is clearly produced by exposure to severe stressors (McEwen, 1998). Additionally, prolonged chronic stressors can alter the brain, disturb cognition and performance, increase susceptibility to disease and mental disorders, and dramatically decrease the quality of life in humans (Baum & Posluszny, 1999; Kim & Diamond, 2002). Thus, chronic stressors have many debilitating effects which can persist long after the actual period of stress exposure (Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002).

3.1 Yerkes-Dodson Law

The Yerkes-Dodson Law expresses an empirical relationship between stress and performance. This law demonstrates that variations in stressor intensity affect performance level (Yerkes & Dodson, 1908). The process is often illustrated graphically as a curvilinear, inverted U-shaped curve which increases and then decreases with higher levels of arousal. Essentially, performance improves with increases in arousal up to an optimal point and then declines with further increases. This law provides a very general description of the relationship between stress and cognitive function. Thus, a small amount of stress can be beneficial for animal performance, but a large amount of stress is detrimental.

3.2 Stress and the HPA Axis

Stress is characterized by physiological changes that occur in response to novel or threatening stimuli (either a real or perceived threat), which causes a cascade of neuroendocrine events within the body. An exposure to stress produces arousal in the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal axis (HPA axis), which causes outcomes such as reduced problem solving and declined task performance (Baum & Posluszny, 1999). The activation of the HPA axis produces disruption to both peripheral and neural systems because it represents an organism's response to a threatening stimulus (Mashoodh, Wright, Hebert, & Perrot-Sinal, 2008). An additional physiological change that occurs in response to stress is the release of glucocorticoids (GC's) by the adrenal glands (Jacobson & Sapolsky, 1991). Prolonged stress exposures and elevated GC levels (cortisol in humans and corticosterone in rodents) can cause detrimental effects on the brain, such as damage to the hippocampus (Bowman, et al., 2001; Kim & Diamond, 2002).

3.3 Stress and the Hippocampus

The hippocampus, involved with learning and memory, has the highest concentration of GC receptors in the brain and is involved in the stress response. Extensive research has demonstrated that the hippocampus is both crucially involved in memory formulations and is highly sensitive to stress (Kim & Diamond, 2002). Chronic stress can lead to changes in the brain, which may produce cognitive impairments or affective disorders by altering brain morphology (Vyas, Pillai, & Chattarji, 2004). The hippocampus, CA3 region in particular, is especially sensitive to high GC levels (McEwen, Gould, & Sakai, 1992; McEwen, Magarinos, & Reagan, 2002; Woolley, Gould, & McEwen, 1990). High GC levels can trigger the death of neurons in the hippocampus (Sapolsky, 1996; Sapolsky, Krey, & McEwen, 1986). GCs can have

devastating actions on the hippocampal pyramidal neurons by inhibiting their glucose uptake, removing their ability to produce adequate amounts of adenosine tri-phosphate (ATP), leading to atrophy and ultimately cell death (Sapolsky, 1990). This inhibits long term potentiation in the hippocampus, modifying neuronal plasticity and contributing to memory impairments (Kim, Song, & Kosten, 2006). Additionally, chronic stress leads to suppressed neurogenesis by causing atrophy of pyramidal CA3 apical dendrites in the hippocampus (Joels, et al., 2004; Magarinos & McEwen, 1995; Watanabe, Gould, & McEwen, 1992). Elevated stress levels also block hippocampal long-term potentiation, which is important for learning and memory (Foy, Stanton, Levine, & Thompson, 1987).

3.4 Stress and the Amygdala

The amygdala is an essential component to the neural circuitry underlying stress and anxiety. As part of the limbic system, the amygdala plays a primary role in the processing and memory of emotional reactions such as fear. The amygdala turns on the stress response in the body by increasing adrenaline and adrenocorticotropic hormone (ACTH) that produces cortisol. Cells in the amygdala have shown to increase after exposure to chronic stressors (Pawlak et al., 2003). Changes in the amygdala can lead to affective aspects of stress disorders (i.e. flattened affect) (Vyas, et al., 2004). Additionally, damage to this region can cause flattened affect through amygdala-frontal dissociation as demonstrated by a reduced emotional response to negative pictures in human studies.

3.5 Stress and the Medial Prefrontal Cortex

The prefrontal cortex is involved in a number of higher cognitive functions as well as processing emotion, decision making, and regulation of stress responses. This area of the brain is a target for GC's involved in the stress response. More specifically, the medial prefrontal

cortex is highly activated by chronic stress and modulates autonomic and neuroendocrine function (Sullivan & Gratton, 1999). Chronic restraint stress alters dendritic morphology in the rat prefrontal cortex and contributes to stress-induced changes in cognition (Cook & Wellman, 2004). Additionally, alterations in the medial prefrontal cortex are linked with hypothalamopituitary adrenal (HPA) axis dysregulation, altered stress hormone levels, and psychiatric symptoms of stress-related mental illnesses (Radley et al., 2007). The prefrontal cortex of the rat is involved in controlling the stress-induced activation of the HPA axis and in mediating negative feedback regulation during times of stress (Sullivan & Gratton, 2002).

4.0 ANIMAL PERFORMANCE AND MODELS OF STRESS

As with the concept of stress, animal performance covers a broad spectrum of areas. For the purpose of this literature review, animal performance refers to the objective outcomes of various behavioral tests for spatial memory, anxiety, and depression. Spatial memory refers to a type of cognitive map, or an organism's recollection of spatial orientation and environment. Anxiety refers to the emotional anticipation of a probable aversive event that is difficult to predict and control (Doron & Parot, 1991). Lastly, depression refers to a misconception of cognitive information, leading to a loss of control, learned helplessness, anergia (inactivity), and anhedonia (lack of pleasure) (Vollmayr, 2003).

4.1 Models of Animal Stress

Four chief models of animal stress include 1) social stressors, 2) physical stressors, 3) a combination of stressors, and 4) the administration of the stress hormone corticosterone (CORT). Social stressors induce a psychological strain on animals. Animal models of social stressors include predator, subordination, novel environment, isolation, and witness stress. For a review

of social stressors, refer to (Vendruscolo, 2006; Pijlman, Wolterink, & Van Ree, 2003; or Krugers, et al., 1997). Meanwhile, physical stressors induce a corporal strain on animals. Animal models of physical stressors include restraint stress, forced swim test, intermittent swim stress, hot or cold temperatures, vibration, hypoxia, or footshocks. For a review of physical stressors, refer to (Christianson & Drugan, 2005; Metz, Schwab, & Welzl, 2001; or Pijlman, et al., 2003).

Chronic mild stress (CMS) (Vollymayr, 2003; Kim, et al., 2003; Mineur, Belzung, & Crusio, 2007; Willner, 1997), chronic variable stress (CVS) (Zurita, Martijena, Cuadra, Brandao, & Molina, 2000), or chronic unpredictable stress (CUS) (Matuszewich, et al., 2007) utilize a combination of social and physical stressors. CMS and CVS are frequently used as proficient models of depression, because they can produce anhedonia and learned helplessness in animals. These models use a variety of intermittent stressors such as plastic restraint tubes, shaker stress, warm or cold water swim, overnight social crowding, vibration, isolation, soiled cages, cage tilt, footshock, change of cage partner, etc. (Ostrander, Ulrich-Lai, Choi, Richtand, & Herman, 2006; Herman et al., 1999; Vollymayr, 2003). Additionally, CUS serves as a primary model for anxiety and can be further divided into unconditioned and conditioned responses.

Researchers can also mimic the stress response by injecting CORT into an animal. The repeated CORT-injection model appears more effective than other modes of delivery (such as the CORT pellet implantation or CORT in drinking water) (Gregus, et al., 2005). CORT injections have produced symptoms of both depression and anxiety as a chronic stressor (Gorzalka & Hanson, 1998; Stone, Egawa, & McEwen, 1988).

5.0 EFFECTS OF CHRONIC STRESS ON PERFORMANCE

5.1 Chronic Stress, Spatial Learning, and Memory

The administration of CORT has been shown to produce a wide variety of effects on rodent performance across several behavioral tests of spatial learning and memory. Chronic CORT treatments impair performance on the Y-Maze (Conrad, Galea, Kuroda, & McEwen, 1996) and the Barnes Maze in young rats (McLay, Freeman, & Zadina, 1998). However, effects of chronic CORT treatments appear to vary according to age: middle-aged rats have impaired performance on the Morris Water Maze (MWM), as demonstrated by a reduced latency to platform, while young rats have no effect from CORT injections on MWM performance (Bodnoff, et al., 1995). For a review on MWM, stress, and memory refer to (D'Hooge & De Deyn, 2001) or (Holscher, 1999). Lastly, chronic CORT treatments do not affect rodent performance on the Barnes Maze (Bardgett, Newcomer, & Taylor, 1996), which contrasts the findings from McLay and colleagues (McLay, et al., 1998). However, Tianeptine (trade name Stablon, Coaxil, or Tatinol) pretreatment reverses the detrimental effects of CORT in the Y-Maze, by restoring hippocampal serotonin levels to equilibrium (Conrad, et al., 1996).

Chronic physical stressors also have a diverse effect on rodent performance across several behavioral studies evaluating learning and memory. Different levels of chronic stress produce different effects. More specifically, chronic restraint stress enhances male rat performance on the Radial Arm Maze (RAM) after two weeks (Luine, Martinez, Villegas, Magarinos, & McEwen, 1996), while three weeks of the chronic restraint stress and the forced swim impairs male rat performance on the RAM (Luine, Villegas, Martinez, & McEwen, 1994; Nishimura, Endo, & Kimura, 1999). It is interesting to note that changes in spatial memory performance in the male rats after three weeks of chronic stress appear temporarily constrained and are reversible (Luine, et al., 1994). Meanwhile, female rats stressed for three weeks under

the same conditions show enhanced spatial memory performance on the RAM (Bowman, et al., 2001). Thus, while sexual and chronic stress exposures differences do exist, the effects of chronic physical stress can be reversed.

Lastly, chronic social stressors on male rodents produce spatial memory impairments in behavioral test performance in both the RAM and the Barnes Maze (Krugers, et al., 1997; Park, Campbell, & Diamond, 2001). Predator stress with a cat and subordination stress with a dominant rat produces deficits in spatial memory and learning.

It is important to note several constraints for the above mentioned behavioral tests. One criticism of the RAM test includes the positive reward at the end of the RAM. Food may confound the results of the study, because it can act as a novel stressor for subjects that lost weight due to stress (Beck & Luine, 1999). Extensive behavioral training is also needed for the RAM, so the stress effects can diminish over time (Beck & Luine, 1999). Regarding the MWM, researchers caution against the interpretation of stress using this paradigm because of the stressful nature of the behavioral test itself (McLay, et al., 1998).

Overall, the four tests of spatial memory (MWM, RAM, Y-Maze, and Barnes Maze) have mixed results on the effects of chronic stressors on rodent performance according to sex, age, and length of chronic stress exposure. Chronic stressors produce an impaired effect or no effect on spatial memory and learning for male rodents, and improved spatial memory for female rodents across several behavioral tests. Most studies utilize male rodents instead of female rodents because of the effect of the proestrus cycle in female rats; therefore differentiating the effects of stress on gender is difficult.

5.2 Chronic Stress and Anxiety

Chronic physical stressors are anxiogenic (i.e. causes anxiety) in rodent performance across several behavioral tests. Male rats exposed to chronic physical stressors (i.e. footshocks or restraint stress) exhibit increased anxiety-like behaviors in the Open Field Test, as demonstrated by increased immobility (Pijlman, et al., 2003; Van den Berg, et al., 1998; Westenbroek, et al., 2005); and the Elevated Plus Maze (EPM), as shown by reduction in open arm exploration (Adamec, et al., 2001; Gameiro, et al., 2006; Vyas, et al., 2004). For a review on the Open Field Test or the EPM refer to (Ramos & Mormede, 1998; Calvo-Torrent, Brain, & Martinez, 1999; Carobrez & Bertoglio, 2005; Gregus, et al., 2005; Ramos & Mormede, 1998; Rodgers & Dalvi, 1997; Wall & Messier, 2001; or Matz, 2006, respectively). One method to combat the increase in anxiety from chronic physical stress includes pair-housing male rats with unstressed female partners, a form of social support (Westenbroek, et al., 2005). Flouxetine (trade name Prozac) also has an analgesic effect on stress for rodents on the EPM (Gameiro, et al., 2006).

While chronic physical stressors consistently produce an increase in the stress response across several behavioral tests, chronic social stressors have varying results. Chronic social stressors (in the forms of predator stress and witness stress) produce an increase (Pijlman, et al., 2003; Van den Berg, et al., 1998) and decrease (Park, et al., 2001) in locomotor activity in the Open Field Test. A decrease in activity in the Open Field Test indicates an increase in stress-like behaviors, while an increase in activity indicates a decrease in stress-like behaviors.

The combination of both physical and social stressors on rodents produce an increase in anxiety-like behaviors in rodent performance in the open field test (Tannenbaum, Tannenbaum, Sudom, & Anisman, 2002), social interaction test (Tannenbaum, et al., 2002), EPM (Hill & Gorzalka, 2004; Zurita, et al., 2000), and acoustic startle test (Zurita, et al., 2000). Apparently,

Naltrexone (trade name Revia or Depade) pretreatment remedies the effect of chronic variable stress on the EPM (Zurita, et al., 2000). However, mild unpredictable stress does not affect rodent performance in the social interaction test (D'Aquila, Brain, & Willner, 1994). Additionally, CORT injections do not affect rodent performance on the open field test or the social interaction test (Gregus, et al., 2005).

Overall, these five tests of anxiety (Open Field Test, Social Interaction Test, Elevated Plus Maze, Light Dark Box Test, and the Acoustic Startle Test) found varying results. The majority of studies found anxiogenic effects of chronic stress on rodents (especially with physical stress and chronic variable stress), while several studies found contrasting effects with social stress or no effects from CORT injections. These disparities could be caused by different test methods, subjects, age or sex of subjects, or human error.

5.3 Chronic Stress and Depression

Chronic stressors induce depression in rodents across many behavioral tests of learned helplessness. More specifically, chronic physical stressors (in the form of the cold water swim stress and mild foot shocks) induce a long-term decrease in depression in rodents as shown by increased immobility in the Forced Swim Test (Christianson & Drugan, 2005), an increased latency to escape in the Swim Escape Test (Christianson & Drugan, 2005), and a decrease in preference for saccharine in the Saccharine Preference Test or anhedonia (Pijlman, et al., 2003).

Chronic social stressors (in the forms of predator stress) induces a long-term decrease in depression as demonstrated by a lower level of sucrose intake in the Sucrose Intake Test (Calvo-Torrent, et al., 1999). It is interesting to note that only one study found an increase sensitivity to reward in the Saccharine Preference Test after chronic physical stress: physical stress causes anhedonia while emotional stress causes an increase sensitivity to reward (Pijlman, et al., 2003).

Chronic unpredictable stress produces a decrease in mobility in the Forced Swim Test (Tannenbaum, et al., 2002), and a decrease in consumption of sucrose in the Sucrose Intake Test (D'Aquila, et al., 1994; H. Kim, et al., 2003; Konkle, et al., 2003; Zurita, et al., 2000). Repeated CORT injections also produce depression-like behaviors in the Forced Swim Test (Gregus, et al., 2005). However, CORT injections warrant further investigations as an animal model of stress, because studies in the past demonstrate mixed results due to habituation, restraint-induced changes, or procedural differences (Gregus, et al., 2005).

Overall, the five behavioral tests of depression or learned helplessness (Forced Swim Test, Swim Escape Test, Shuttle Escape Test, Sucrose Intake Test, and Saccharine Preference Test) predominantly demonstrate an increase in rodent depression following chronic stress. However, stress can cause varying long-term effects depending on the stress modality. Social stress decreases depression in some instances, while physical stress increases depression in other situations.

6.0 DISCUSSION

A variety of conclusions can be made from the above findings. Chronic stressors do, in fact, affect rodent performance in tests of spatial learning, anxiety, and depression in both positive and negative ways. Several additional findings arose from this literature review of the effects of chronic stressors on rodent performance. These findings were used to design the Bioscience and Performance Division's research portfolio in cognitive performance under stress.

6.1 Stress Model

In order to effectively study the effects of chronic stressors on animal performance, a specific stress model is needed for each type of animal stressor (i.e. social, physical, combination

of social and physical, or CORT) with gradable stress effects. Essentially, the dimensions of stress paradigms and intensity differ in impact. While many types of stress paradigms do exist, they ignore the relationship between the intensity, duration, type of nociceptive model used, and type of stressor.

Currently, few attempts exist at obtaining a gradable stress effect in social stress models (Zelena, 1999). The visible burrow system (VBS) is the only known hierarchy model that demonstrates different levels of stress. This model has been used to study the aggression of male rats in a social context (Tamashiro et al, 2004). The VBS colony model enables rat groups to produce natural stressful social interactions that constitute a relevant model for analyzing behavioral, neural, and endocrine correlates of chronic stressors (Blachard et al., 1995). In this setting, consistent asymmetries in offensive and defensive behaviors of male dyads are related to the development of dominance hierarchies. Male subordinate rats are characterized by wound patterns, weight loss, and behavioral changes (i.e. depression).

The severity of each type of stressor should be considered, because different intensities produce different performance outcomes on behavioral tests. Different stress modalities (physical vs. social stressors) produce different results for anhedonia (Pijlman, 2003; & Van den Berg, 1998). Each animal stress model should account for the whole spectrum of results that can occur. For example, an animal model based on physical stressors should account for a low intensity, medium intensity, and high intensity of physical stress, along with different time increments of physical stress duration. Humans in particular react differently to stress depending on the type of stressor, intensity, or duration of stressor but also in regards to subject variables (dispositional factors, age, personality, copy styles, etc.) (Zelena, 1999).

6.2 Sex Differences

A separate animal stress model is necessary for both sexes. Many animal models of stress disregard female rodents altogether because of the effect of the female proestrus cycle. However, females react differently from the widely accepted fight or flight stress response. Females *tend and befriend*, where tending refers to nurturing that protects the self and offspring, and befriending refers to creating and maintaining social networks (Taylor, 2000). Behavioral tests of spatial learning and memory demonstrate the largest differences in male and female behavior: chronic stress reduces spatial memory in male rats, but improves spatial memory in female rats (Bowman, 2001). Additionally, females are twice as likely to suffer from anxiety or depression as males, so it is important to study sex results to resolve connections between chronic stress and affective disorders (Kendler, 2001; Kessler et al., 1993; Altemus, 2006). Female rodents demonstrate several other related differences: they produce faster rates of weight gain and have higher hippocampal glucocorticoids receptor levels than stressed male rodents (Konkle, 2003; Figueiredo, 2002; Handa, 1994). Males and females react to stress differently, so two models should exist to capture these variations. Researchers need to terminate the sex bias used in animal models of stress.

6.3 Habituation

Due to the stressful nature of the various behavioral tests, one has to have an awareness of how acclimation, pre-handling, and the order of tests affect test results. Habituation can be problematic when studying chronic stress. Repeated exposure to the same stressor may reduce the effects of the stressor (Koolhass, 1997; Gamaro, 1998). Several ways to remedy this effect may include using an assortment of stressors, minimizing handling, or ordering the behavioral tests according to their level of stress.

6.4 Social Stress

While a variety of animal stress models exist; social stress remains the most robust model for studying the effects of chronic stress on rodent performance. Psychosocial factors are among the most powerful of stressors, such as new experiences, predator stress, anticipation of punishment, etc. (Mason, 1975). Social stress models are preferred over physical stress models because animals do not encounter physical stressors in their natural environment. Animals should be studied under naturalistic social conditions, where automatic reactions and behaviors can be recorded (Stephanski, 2001). Predator stress serves as an ideal model of social stress because it is ecologically relevant for an animal's survival and produces reactions similar to those found in natural surroundings (Mashoodh, 2008; Calvo-Torrent, 1999). More importantly, humans are much more likely to be repeatedly exposed to social stressors, causing psychological harm in the form of depression or anxiety (Mashoodh, 2008). A more naturalistic animal model of stress can mimic the biology of the species and allow for an analysis of etiology and symptomology. Thus, social stress is the most common and practical model of stress that both humans and animals face (Blanchard, 2001).

6.5 Drug Solutions

It is important to highlight that some effects from chronic stressors are reversible, so it is imperative to further evaluate the possible solutions to combat the effects of chronic stress. Drugs such as Tianeptine, Flouxetine, and Naltrexone reduced the negative effects of chronic stressors. However, the most unorthodox remedy includes social support. Pairing stressed male rats with unstressed female rats drastically decreases levels of anxiety (pairing stressed males with unstressed males has not been addressed). Thus, social support networks can be further investigated to combat the role of anxiety in animals and humans, as a type of sex reward effect.

Social support networks also serve as a form of enrichment. Environmental enrichment, the provision of an unusually rich and stimulating environment, can produce lasting morphological and biochemical changes in the brain, and has been shown to protect against and reverse the effect of various stressors. Additionally, some studies suggest environmental enrichment causes rats to not seek sucrose or drug rewards as readily as socially housed control rats (Stairs, Klein, & Bardo, 2006; Wood, Segal, & Rebec, 2006).

6.6 Future Research

Several potential areas to explore regarding behavioral tests and chronic stressors include comorbidity, aggression, sensory-motor tests, non-spatial learning or nociception. For example, anxiety is a frequent co-morbid feature of depression and should be studied further (Tannenbaum, 2002). By evaluating this wide range of behavioral test categories, researchers can increase their knowledgebase of how humans and animals react to stress. Increased knowledge of reactions to stressors can help humans adapt to their environment more effective. This increased knowledge may also help create a working model for evaluating the pharmacology of new drugs or for understanding the neurobiological underpinnings of a disorder.

7.0 CONCLUSION

An overarching theme across the literature review findings is that chronic stressors produce an inconsistent effect across rodent performance and that the stress paradigms differ in impact. Chronic stressors in the form of social stressors, physical stressors, a combination of both social and physical stressors, and the administration of the stress hormone corticosterone have a diverse effect on various measures of animal performance. A variety of factors exist for

evaluating the effects of chronic stressors such as the type and duration of stressor, rodent strains, rodent ages, varying sex reactions, habituation, etc. By having an awareness of these different factors, researchers can improve the current animal models of stress. This literature review concluded the following: a specific disease model is needed for each type of animal stressor with gradable stress effects, distinct sex differences exist among rodents, habituation is a reoccurring problem in rodent behavioral testing, social stress remains the most robust model for chronic stress, several effects of chronic stress are reversible via drugs or enrichment, and many potential areas exist to explore for animal behavioral tests. Having an awareness of these current issues in animal research is critical for understanding how animals react to stress. By fully understanding how rodents operate both physiologically and psychology, researchers can increase the quality of life for humans by combating the effects caused by chronic stressors. The military can especially utilize this information to improve the performance of soldiers facing chronic stressors in a deployed environment. Specifically, one of the goals of the Bioscience and Performance division is to address stress-related cognitive impairments and identify countermeasures. A representative animal model of stress is necessary to develop solutions for our Airmen and improve performance under stress.

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